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EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/802,445	Applicant(s) VAN NEST	
	Examiner Daniel Sullivan	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This action is a response to the Amendment and Response Under 37 C.F.R. §1.111 (Paper No. 13) filed July 3, 2002. Claim 1, as amended in Paper No. 13, and claims 2-22 are pending in the application.

Claim Rejections - 35 USC § 112

Rejection of claims 1-8 under 35 U.S.C. §112, first paragraph, in Paper No. 9 is withdrawn in view of the amendment of claim 1, which is now drawn to "[a] method of delaying development of a symptom of papillomavirus infection". As stated on page 3, paragraph 1, of the cited office action, "the disclosed use is limited to reducing the severity of...a symptom of papillomavirus infection". The scope of the amended claim is within this disclosed use.

Rejections of claims 9-22 under 35 U.S.C. §112, first paragraph, is also withdrawn.

Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing severity of a symptom of papillomavirus infection in mice, dogs, rabbits and humans with papillomavirus, by administering a polynucleotide comprising an immunostimulatory sequence to said mice, dogs, rabbits and humans at a dose sufficient to reduce the severity of a symptom of papillomavirus infection, wherein the ISS comprises the sequence 5'-CG,pyrimidine, pyrimidine, CG, does not reasonably provide enablement for a method of reducing the severity of a symptom of papillomavirus infection in any individual or mammal. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention: The claims are drawn to methods and compositions to be used in the treatment of papillomavirus infection, said methods and compositions comprising ISS sequences.

The breadth of the claims: Given their broadest reasonable interpretation, the claims encompass methods and compositions for treatment of papillomavirus infection in all individuals and mammals wherein the composition comprising the ISS sequences is administered in an amount sufficient to delay development of papillomavirus infection.

The state of the prior art and level of predictability in art: The use of CpG sequences as an immunostimulatory adjuvant is well know in the art. However, according to the teachings of Agrawal and Kandimalla (*Trends. Mol. Med.* (2002) 8:114-121), published well after the effective filing date of the instant application, "Although the presence of an unmethylated CpG dinucleotide is essential for the induction of an immunostimulatory activity, the sequences

flanking the CpG dinucleotide also play a role", human immune cells respond poorly to the hexameric motif found to be optimal in activating the mouse immune system "suggesting that the sequences required for CpG-related immune stimulation varies from species to species" and "the optimal CpG sequence requirement for many other animal species is not known" (beginning page 114, column 2 final paragraph and continued through the first paragraph of page 115). These comments demonstrate the high degree of uncertainty in the art with regard to extending results obtained in one species to other species. The prior art is silent with regard to the effectiveness of CpG oligonucleotides in stimulating immune responses in individuals outside of the genus *mammalian*; however, the variability among mammalian species provides a high degree of uncertainty in extending results obtained with mammals to another genus.

The amount of direction provided by the inventor and the existence of working examples: Both the prior art and the inventor provide direction and working examples that would enable one of ordinary skill in the art to practice the invention in a limited number of mammalian species. However, because there is a high degree of variability in the effectiveness of CpG oligonucleotides at stimulating the immune system of different mammalian species, it is not possible to extend these teachings to species other than those for which working examples already exist (i.e. rabbit and dog, taught in the instant application; mouse and human, taught in the prior art).

Relative skill of those in the art: The level of skill in the relevant art is very high. However, because the structural determinants dictating the function of CpG sequences in individual mammalian species are unknown, the prior art does not enable the skilled artisan to extend the explicit teachings found there without significant empirical experimentation.

The amount of experimentation required to practice the invention: Agrawal and Kandimalla (*supra*) teach, "Studies on the medicinal chemistry of CpG DNA have just begun..." and "There is a species-dependent selectivity of CpG DNA, and the optimal CpG DNA sequences for many vertebrate species are not known yet. Medicinal chemistry could help to resolve the issues of species-selective bias of CpG DNA motifs and permit the application of CpG DNA therapeutics for treating veterinary diseases without requiring the identification of optimal sequences for each species" (page 119, column 2, first and second paragraphs of the Concluding Remarks). These remarks show that practicing the claimed invention commensurate with its full scope would require the skilled artisan to identify, through empirical experimentation, an oligonucleotide sequence that can effectively stimulate the immune system of any and all individuals or identify the structural determinants that dictate the species specificity of CpG immunomodulation. This amount of experimentation would place an undue burden on one seeking to practice the invention commensurate with the full scope of the claims.

Thus, due to the art recognized unpredictability of obtaining stimulation of immune responses using CpG oligonucleotides and the lack of guidance in the specification or prior art with regard to how to use the invention in all individuals, it would require undue experimentation to practice the invention commensurate with the full scope of the claims.

Claims 9-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method and compositions for reducing severity of a symptom of papillomavirus infection wherein the administration is at the site of a papillomavirus lesion, is

not enabling for a method and compositions wherein the composition is administered prior to the development of a lesion or outside of the affected area.

The nature of the invention and the relative skill of those in the art are described above.

The breadth of the claims: The claims encompass a method of reducing severity of a symptom of papillomavirus infection wherein a composition comprising a CpG oligonucleotide is administered to an individual who has been exposed to papillomavirus at any time point after exposure, and wherein the composition is administered to the individual at any site and by any route.

The state of the prior art and level of predictability in the art: As described above, the relevant art is at an early stage of development and many of the factors dictating the effectiveness of immunostimulation obtained with CpG oligonucleotides remain to be established. With regard to the effectiveness of systemic administration of CpG oligonucleotides and their administration without antigen, the prior art teaches that the effectiveness of immunostimulation with CpG oligonucleotides is dependent on the proximity of the antigen to the site of administration of the oligonucleotide. Weiner et al. (IDS #127) teach that, "Injection of CpG [oligonucleotide] and antigen on the same flank was required for maximal adjuvant effect. Thus, CpG [oligonucleotide] exerts much of its adjuvant effect locally. This finding is consistent with or prior observations that footpad injection with CpG [oligonucleotide] enhances NK activity of cells in the ipsilateral but not contralateral lymph node" (see page 10834, column 1, final paragraph through the first paragraph of column 2 and Figure 4 and the caption thereto). This teaching introduces uncertainty as to whether "an amount sufficient to prevent a symptom of papillomavirus infection" could be achieved in embodiments of the instant invention wherein

the CpG oligonucleotide is administered away from the site of antigen. Because the claimed invention is drawn to administration of the CpG oligonucleotide without antigen, antigen is provided by the active infection at the site of the lesion and therefore the teachings of the prior art introduce uncertainty as to whether the invention would be operable when CpG oligonucleotides are administered away from the lesion. With regard to administration prior to the development of a lesion, the prior art is silent with regard to the effectiveness of CpG oligonucleotides administered in the absence of antigen but in the presence of the early stages of viral infection prior to the development of a lesion. Based on the teachings of the prior art the skilled artisan would not predict that embodiments of the claimed invention wherein the CpG oligonucleotide is administered away from, or in the absence of antigen provided by the active infection to be operable.

The amount of direction provided by the inventor and the existence of working examples: As described above, the prior art provides no working examples of those embodiments of the invention wherein the CpG oligonucleotide is administered away from a source of antigen. The teachings of the prior art suggest that the effectiveness of administration away from the site of antigen is, at best, unpredictable. The specification only describes, in specific terms, embodiments of the invention wherein the CpG oligonucleotides are administered by intradermal injection at the site of inoculation with papillomavirus or at the site of a papillomavirus lesion (see especially Examples 1 and 2). The specification further teaches that administration of the CpG oligonucleotides at 1 and 14 days following inoculation with papillomavirus is not effective at reducing the severity of a symptom of papillomavirus infection. (see especially figure 2, panels A and C). These teachings do not provide the skilled artisan with the guidance required to

practice the invention commensurate with the full scope of the claims and, in fact, introduce additional uncertainty as to how to practice embodiments of the invention wherein the CpG oligonucleotide is administered at early time points following papillomavirus infection.

The amount of experimentation required to practice the invention: Practicing the full scope of the claimed invention would require the skilled artisan to devise a means to delay development of a symptom of papillomavirus infection by administering a CpG oligonucleotide, without co-administration of an antigen, at sites other than those directly affected by papillomavirus or at time points prior to the development of a lesion. The teachings of both the prior art and specification indicate that there are barriers to accomplishing this, but neither provides guidance as to how these barriers can be overcome. The skilled artisan would therefore have to engage in empirical experimentation to develop a means to administer an amount of CpG oligonucleotide at all locations and at all time points following papillomavirus infection in an amount sufficient to delay development of a symptom of papillomavirus infection.

Thus, due to the uncertainty provided by the teachings of the specification and prior art with regard to delaying development of a symptom of papillomavirus infection by administration of a CpG oligonucleotide, without co-administration of an antigen, away from the site of papillomavirus exposure and prior to development of a papillomavirus lesion, and the absence of teachings with regard to how to overcome the barriers to achieving effective immunostimulation in the absence of antigen, practicing the claimed invention commensurate with its full scope would place an undue burden of empirical experimentation on the skilled artisan.

Claim Rejections - 35 USC § 102

Rejection of claims 19 and 20 under 35 U.S.C. 102(b) as being anticipated by Dartmann et al. is withdrawn. As pointed out in Applicant's response (page 12), the nucleotide sequence taught by Dartmann does not anticipate the claimed nucleotide sequence.

Claims 17, 18, 21 and 22 stand rejected under 35 U.S.C. 102(b) as being anticipated by Dartmann. Applicant's arguments regarding this rejection have been fully considered but were not found to be persuasive.

The sequence cited by the examiner is found at positions 719-726 in Figure 1. First, Applicant argues that Dartmann does not disclose a composition comprising a polynucleotide comprising the claimed ISS. Applicant is directed to the first column of page 124 wherein Dartmann cites descriptions of the cloning and sequencing of HPV11 DNA, which the skilled artisan would understand requires possession of a composition comprising a polynucleotide to be sequenced.

Applicant also argues that the art does not anticipate the claims because Dartmann does not disclose a kit comprising the composition, nor a kit that does not comprise a papillomavirus antigen and comprising instructions for administration of the composition.

Although Dartmann does not explicitly teach a composition that does not comprise a papillomavirus antigen, the skilled artisan would know that the composition comprising a cloned polynucleotide of sufficient purity for sequencing taught by Dartmann would not comprise a papillomavirus antigen. With regard to the instructions, the examiners assertion on page 9 of the Office action that, "mere printed matter cannot impart a patentable feature on a claim" and citation of *In re Gulack* 217 USPQ 401 (1983) are proper. Applicant asserts that the decision in

In re Gulack provides that the inclusion of instructions for use as a component of a composition should be afforded patentable weight, particularly pointing that, "[d]ifferences between an invention and the prior art cited against it cannot be ignored merely because those differences reside in the content of printed matter" and "the board cannot dissect a claim, excise the printed matter from it, and declare the remaining portion of the mutilated claim to be unpatentable..". While it is true that the Court held that printed matter *can* carry patentable weight, the Court states that "[w]here the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the art in terms of patentability". Applicant argues that the instructions for administering the composition are functionally related to the composition comprising an ISS to be administered (page 14) but does not provide an explanation of how function of the composition is altered by the presence of instructions. There is no reason to believe that the composition taught by Dartmann would not be functional in the treatment of papillomavirus infection simply because it was not packaged with instructions. Therefore the composition taught by Dartmann anticipates all of the patentable limitations of the instant claims.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 17-19, 21 and 22 are rejected under 35 U.S.C. 102(a) as being anticipated by Schwartz (1999; IDS #32).

The claims are drawn to a kit for use in the treatment of papillomavirus infection comprising a composition comprising a polynucleotide comprising an ISS, wherein the ISS comprises the sequence 5'-C,G,pyrimidine,pyrimidineC,G-3', wherein said kit does not comprise a papillomavirus antigen. As indicated above, the instructions for administration of said composition have not been given patentable weight. Claim 18 limits the ISS to a sequence comprising 5'-purine,purine,C,G,pyrimidine,pyrimidine,C,G-3' and claim 19 limits the sequence of claim 18 to 5'-AACGTTCG-3' or 5'-GACGTTCG-3'. Claim 21 limits the papillomavirus to a human papillomavirus and claim 22 limits the papillomavirus to an animal papillomavirus.

Schwartz teaches a composition comprising the nucleotide sequence 5'-AACGTTCG-3' or 5'-GACGTTCG-3' (see especially page 10, third full paragraph). The composition taught by Schwartz is the same as the composition claimed in the instant application; therefore the teachings of Schwartz anticipate the claims.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejection of claims 9-22 under 35 U.S.C. § 103 is withdrawn. Regarding the method claims, none of the cited art teaches that the CpG oligonucleotide should be administered without antigen or suggests that administration without co-administering antigen would be desirable. Therefore the skilled artisan, at the time the application was filed, would have had neither the instruction nor the motivation to omit antigen from the administered compositions taught by the prior art. With regard to claims 19 and 20, as indicated above, the claims are drawn to

polynucleotides comprising nucleic acid sequences that are neither taught nor suggested by the cited art.

Rejection of claims 17, 18, 21 and 22 under 35 U.S.C. § 103 is withdrawn because, although the composition would have been obvious to one of ordinary skill in the art at the time the invention was made, the claims are actually anticipated by Dartmann. Therefore the claims are more properly rejected under 35 U.S.C. 102.

Allowable Subject Matter

None of the claims are allowable.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
September 9, 2002

JAMES KETTER
PRIMARY EXAMINER